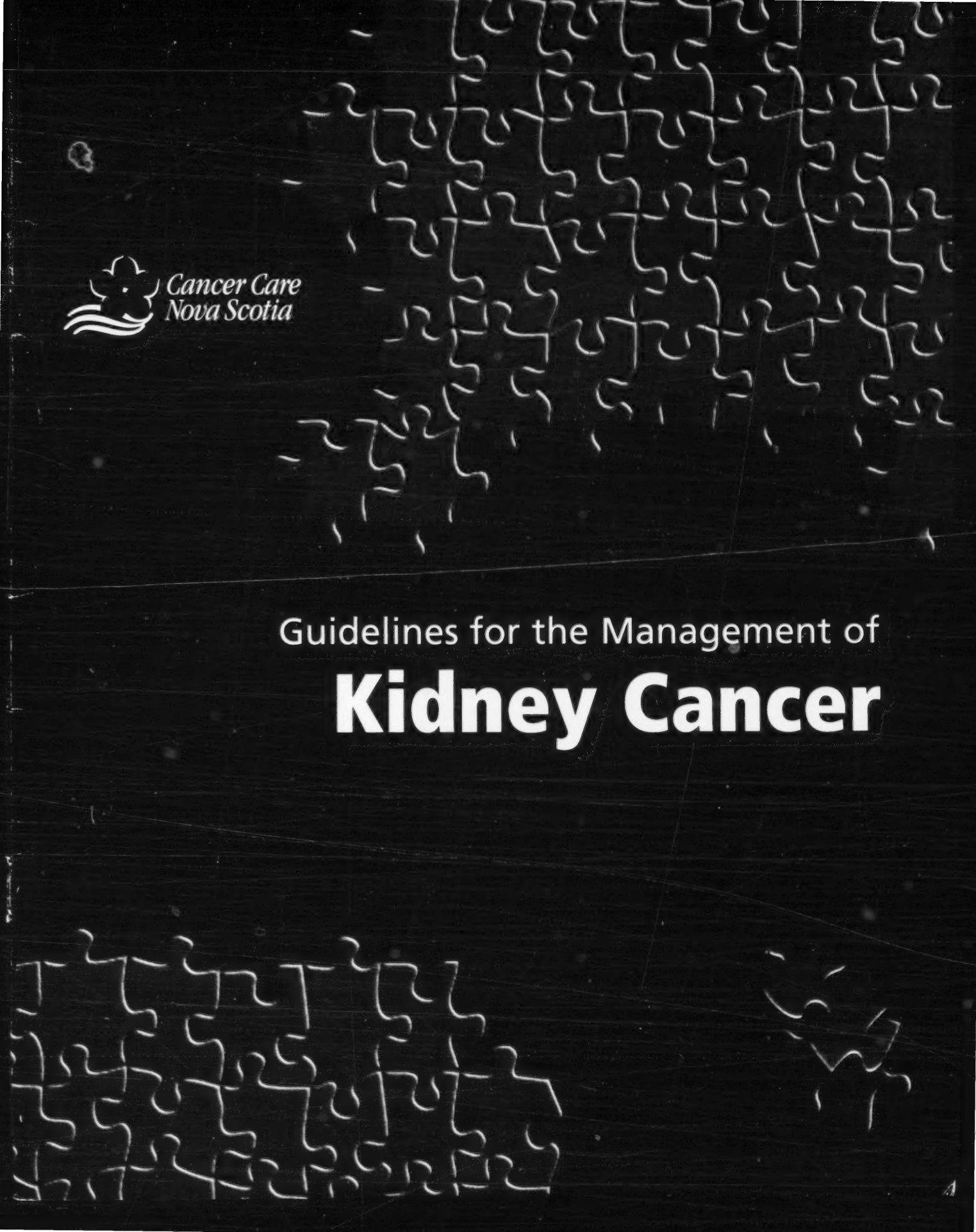

Guidelines for the Management of

Kidney Cancer

104-05530/

Guidelines for the Management of

Kidney Cancer

Cancer Care
Nova Scotia

Guidelines for the Management of Kidney Cancer

Objective:

This guideline reviews the overall management (from initial presentation and diagnosis through referral, treatment and follow-up) of kidney cancer in adults in Nova Scotia. It is primarily designed for specialists treating kidney cancer in Nova Scotia.

Other interested physicians (especially family physicians) and health professionals may find the algorithms a useful summary of the management of kidney cancer. Patients, family members and other non-health professionals are encouraged to review materials written specifically for them. The Canadian Cancer Society Information Service (1-888-939-3333 or www.cancer.ca) is one source for this type of information.

Preamble Note:

Practice guidelines are intended to assist health care professionals with decisions throughout the spectrum of the cancer experience. Guidelines should never replace specific decisions for individual patients, and do not substitute for the shared decisions between any patient and physician (or other health professional) which are unique to each circumstance. However, guidelines do provide evidence-based background information, consensus-based recommendations for similar problems, and a context for each individual decision. This guideline will be revised, from time to time, as new evidence becomes available, and reviewed at least every three years. Current versions of this guideline will be available on the *Cancer Care Nova Scotia* website (www.cancercare.ns.ca).

Comment on Clinical Trials:

An important component of treatment decision-making for any patient is the potential for enrollment in a relevant clinical trial. The Genitourinary Cancer Site Team is committed to advancing patient care, through participation in clinical trials. At any point in time, there may be a clinical trial opportunity for any component of this guideline. As specific trials become available, eligible patients may be offered the opportunity to enroll in the relevant trial. Every effort will be made to accommodate patients for clinical trial participation, but there will be eligibility restrictions for each trial. Patients are encouraged to discuss clinical trials opportunities with their cancer specialist. Current clinical trials will be listed on the *Cancer Care Nova Scotia* website (www.cancercare.ns.ca).

Acknowledgements:

This guideline was written by a collaborative effort of the Genitourinary Cancer Site Team, and was sponsored by *Cancer Care Nova Scotia*. Portions of this practice guideline have been adapted from guidelines prepared by the London Regional Cancer Centre (Aug 2001), and the British Columbia Cancer Agency (Jan 2000). The guidelines also incorporate knowledge of current evidence by the cancer experts in Nova Scotia.

For further information on this, or any other Practice Guideline, please contact the Cancer Site Team Co-Chairs, or members of the Guidelines Resource Team, *Cancer Care Nova Scotia* (contact person Michele Moore, phone (902) 473-3152 or by email michele.moore@ccns.nshealth.ca).

Guideline Approvals:

Genitourinary Cancer Site Team -

- Initial date approved - 11 October 2002
- Revision with Community Reviewer Input - 26 May 2003

Cancer Care Nova Scotia, Commissioner

- 08 July 2003

Guidelines for the Management of Kidney Cancer

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Part 1. Introduction

1.1 Risk Factors and Screening

There is no established role for screening the general population for renal cell carcinoma. There is an increased incidence in patients with VonHippel-Lindau syndrome (often at a younger age and often bilateral), and acquired cystic renal disease from dialysis. Screening is advised for patients with VonHippel-Lindau syndrome and their family members, and possibly for patients with acquired cystic renal disease.

1.2 Presentation

Renal cell carcinoma may remain clinically occult for most of its course. The classic presentation of pain, hematuria, and flank mass occurs in only about 20% of patients and often is indicative of advanced disease. Approximately 30% of patients with renal cell carcinoma present with metastatic disease, 25% with locally advanced disease, and 45% with localized disease. Rarely, patients present with paraneoplastic syndromes (hypercalcemia, polycythemia, hypertension, Cushing's syndrome).

Part 2. Histology and Pathology

2.1 Histology

Tumour Classifications

Renal Tumours in Adults

- Renal Adenoma
- Renal Cell Carcinoma
    - Conventional (clear cell) renal cell carcinoma
    - Chromophil renal cell carcinoma
    - Chromophobe renal cell carcinoma
    - Collecting duct carcinoma
- Renal oncocytoma
- Neuroendocrine tumours of the kidney
- Angiomyolipoma
- Hemangioma
- Lymphangioma
- Leiomyoma
- Lipoma
- Leiomyosarcoma
- Liposarcoma
- Malignant Fibrous Histiocytoma
- Rhabdomyosarcoma
- Other sarcomas
- Juxtaglomerular cell tumour
- Renomedullary interstitial cell tumour
- Cystic nephroma
- Metanephric adenoma and Nephrogenic adenofibroma
- Lymphoma
- Metastasis to the kidney

From: Tumors of the Kidney, Bladder, and Related Urinary Structures, AFIP, 3rd Series, Fascicle 11

Pathologic Assessment
While the majority of adult renal cell tumours will be renal cell carcinomas, it is important not to overlook the possibility of a different histology (such as transitional cell carcinoma, lymphomas, or sarcomas) when atypical clinical features are present. These tumours require individualized management.

In patients with advanced or metastatic disease where there is no nephrectomy specimen to confirm the diagnosis, a biopsy of the primary or metastatic site should be obtained to confirm the diagnosis.

2.2 Pathological Description

Radical nephrectomy specimens should include the following information:

2.2.1 Gross description

1. the size of the kidney (three dimensions)
2. the length of the attached ureter
3. the size of any tumour mass and the size of any satellite nodules
4. the location of any tumour masses
5. the relationship to capsule, to the ureter, and pelvis
6. the presence of tumour within the renal vein

2.2.2. Microscopic description:

1. histologic type and grade
2. the invasion of capsule, ureter, pelvis, renal pelvic fat, vessels, extracapsular fat, and renal vein
3. the location of positive margins if present
4. comment on the non-malignant renal parenchyma

2.3 Histopathological Grading

Fuhrman Nuclear Grading System for all Subtypes of Renal Cell Carcinoma

Grade	Characteristics
Grade 1	Round, uniform nuclei approximately 10 µm in diameter with minute or absent nucleoli
Grade 2	Slightly irregular nuclear contours and diameters of approximately 15 µm with nucleoli visible at 400 x
Grade 3	Moderately to markedly irregular nuclear contours and diameters of approximately 20 µm with large nucleoli visible at 100 x
Grade 4	Nuclei similar to those of grade 3 but also multilobar or multiple nuclei or bizarre nuclei and heavy clumps of chromatin

From: Am J Surg Pathol, 1982; 6: 655-63

Part 3. Diagnosis and Staging

3.1 Staging Investigations

1. History and physical examination
2. CBC, liver function tests, BUN, creatinine, calcium and/or alkaline phosphatase
3. Chest X-ray +/- CT scan chest
4. Abdominal US or CT scan abdomen (other diagnostic imaging, as needed)
5. Bone scan (if alkaline phosphatase and/or calcium are elevated or clinical suspicion)
6. CT scan brain (if clinical suspicion)

3.2 TNM Clinical Classification

Primary Tumour (T)

TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
T1 Tumour 7 cm or less in greatest dimension, limited to the kidney
- T1a Tumour 4 cm or less in greatest dimension, limited to the kidney
- T1b Tumour more than 4 cm but not more than 7 cm or less in greatest dimension, limited to the kidney

T2 Tumour more than 7 cm in greatest dimension, limited to the kidney
T3 Tumour extends into major veins or invades adrenal gland or perinephric tissues but not beyond Gerota fascia
- T3a Tumour invades adrenal gland or perirenal and/or renal sinus fat but not beyond Gerota fascia
- T3b Tumour grossly extends into renal vein(s) or its segmental branches or vena cava below diaphragm
- T3c Tumour grossly extends into vena cava above diaphragm or invades wall of the vena cava

pT4 Tumour invades beyond Gerota fascia

Regional Lymph Nodes (N)

The regional lymph nodes are the hilar, abdominal para-aortic, and paracaval nodes. Laterality does not affect the N categories.

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single regional lymph node
N2 Metastasis in more than one regional lymph node

Distant Metastasis

MX Presence of distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

3.3 TNM Stage Grouping

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3a	N0	M0
	T3a	N1	M0
	T3b	N0	M0
	T3b	N1	M0
	T3c	N0	M0
	T3c	N1	M0
Stage IV	T4	N0	M0
	T4	N1	M0
	Any T	N2	M0
	Any T	Any N	M1

From: American Joint Committee on Cancer, AJCC Cancer Staging Manual, Sixth Edition. Springer-Verlag, 2002.

Part 4. Referral Information for the New Patient Visit

A letter of referral and a pathology report documenting the cancer diagnosis are the usual minimal requirements for a referral to a tertiary cancer center. A referral need not be delayed due to incomplete results from tests (either due to test scheduling delays or waiting time for test results).

Referral to the Capital Health/QEII Cancer Care Program

Referrals to the Capital Health/QEII Cancer Care Program (CCP) may be faxed to the Nova Scotia Cancer Centre Referrals Office at 902-473-6079 (tel. 902-473-5140 or 902-473-6098). It is preferred that referrals be accompanied by the CCP Referral form available upon request at the above phone numbers or available for downloading at www.cdha.nshealth.ca/physicianupdate. For urgent or emergent referrals, please page the appropriate specialist on call through the QEII HSC Locating service (902-473-2220) to discuss the referral.

Referral to the Cape Breton Cancer Centre

Referrals to the Cape Breton Cancer Centre may be directed to the referrals/booking office at 902-567-7774 (fax 902-567-7911). For urgent or emergent referrals, please page the appropriate specialist on call through the Cape Breton Regional Hospital Locating service (902-567-8000) to discuss the referral.

Referral to the IWK Health Centre

Pediatric cancers are specifically not covered within this guideline. For these patients, referral calls to the IWK Health Centre may be directed to the pediatric hematologist/oncologist on call at 902-470-8888. For the phone consultation, the following information will be needed: name and age of the patient, parent's phone number, relevant history and physical examination, presumptive diagnosis, and any initial investigation results. Surgical biopsy or other intervention is not recommended until initial contact has been made with the IWK Health Centre pediatric hematologist/oncologist. A summary of history & physical examination and investigation results can be faxed to 902-470-7208. Further diagnostic investigations will be determined after initial contact and discussion.

Referral Information for Adults

Letter of Referral*

A legible referral or consultation letter high lighting presenting signs and symptoms.

Pathology Reports*

a. Needle biopsy
b. Any other diagnostic procedure where a biopsy is taken

Operative Reports (relevant to the cancer- if performed prior to referral)

a. Nephrectomy
b. Other

Diagnostic Imaging Reports*

a. All relevant chest radiographs (films and reports), including old images*
b. Thoracic, abdominal and any other relevant CT scans (films and reports)*
c. Bone scans (films and reports)*
d. Any other relevant diagnostic imaging (films and reports)

Other Information

a. Any relevant consultation reports
b. Renal function test results (if done)*
c. Relevant bloodwork (if done)*
d. Detailed information on any previous chemotherapy or radiotherapy of current malignancy
e. Any information on previous malignancies
f. Information on co-existing medical conditions and allergies

* Specific information which is necessary for proper triage of referrals

Please note: If the referring physician would like to discuss a case with a specialist, feel free to call the appropriate specialist (Radiation Oncology, Medical Oncology, or Urology, by calling 902-473-2220 at Queen Elizabeth II Health Sciences Centre or 902-567-8000 at Cape Breton Cancer Centre - ask for the specialist on call or a specific physician at this number). If any tests or reports are pending, the date of the procedure, and the location of the procedure should be noted, so that the reports may be obtained when available. Send in the referral while awaiting these results, in order to facilitate a timely appointment for your patient.

Part 5. Treatment of Kidney Cancer

5.1 Stage I (T1 N0 M0) and Stage II (T2 N0 M0)

- Radical nephrectomy (open or laparoscopic) with or without regional node dissection.

- Partial nephrectomy in select cases of functional solitary kidneys, small polar lesions or patients with lesions amenable to this procedure.

5.2 Stage III (T1 N1 M0 - T2 N1 M0 - T3 N0,N1 M0)

Surgery
Radical nephrectomy (open or laparoscopic) with or without regional node dissection. Renal vein or vena cava involvement can be surgically excised with curative intent. Patients with bilateral primary renal cell carcinoma or only one functioning kidney may potentially undergo partial nephrectomy.

Radiation Therapy
Radiation therapy has no established role as primary definitive therapy of early renal cancers or as an adjuvant to surgery (preoperative or postoperative).

Chemotherapy or Immunotherapy
Chemotherapy or immunotherapy has no role as adjuvant therapy for high risk tumours.

5.3 Stage IV (T4 N0 N1 M0 - any T N2 M0 - any T any N any M1) or Recurrent Disease

Surgery

1. Palliative nephrectomy or angio-infarction may be required for symptom control or hematuria.
2. Resection of a solitary metastasis (with or without adjuvant radiotherapy) from renal cell carcinoma can be considered if the interval from nephrectomy to the detection of the metastasis is sufficiently long and the metastasis is proved to be solitary by adequate restaging (CT of brain, chest and abdomen, bone scan). Resection of solitary metastasis at diagnosis can be considered on an individual basis.
3. Fully ambulatory patients (with high performance status) with metastatic renal cell carcinoma at diagnosis who are to be treated with interferon-alfa therapy (see below) have a modest survival improvement if they undergo initial nephrectomy, assuming the primary to be readily operable.

Radiation therapy
Radiation therapy may be used to control bleeding and pain from the primary tumour and to palliate symptoms from metastases. Radiation may be considered in select patients with positive surgical margins.

Chemotherapy and Hormonal Therapy
Vinblastine or other chemotherapy agents are no longer recommended.

There is no evidence to support the use of medroxyprogesterone (Provera).

Immunotherapy
Recombinant interferon alfa given by subcutaneous injection has a response rate of about 15% in metastatic disease. It has shown a modest survival improvement, however, it did have a negative impact on quality of life. For patients who want therapy, interferon alfa is a reasonable option to consider (see Appendix 1).

Interleukin-2 is another form of immunotherapy which has been studied in phase I & II trials with response rates ranging from 10-35%. No phase III studies have been conducted to show an improvement in survival, and thus it is not considered to be a standard of care.

Part 6. Follow-up Practice Guidelines

Following the completion of treatment, patients may need to be monitored for potential recurrence of cancer and complications of therapy. It would be useful to have a discussion, in the early stages of treatment planning, about whether a patient would want to know about an asymptomatic recurrence and the limited treatment options available for metastatic disease. If follow-up is chosen by the patient, the schedule below may be used.

Often it is felt appropriate to transfer follow-up to the family doctor, in which case it is important for the patient to be clear who is responsible for certain aspects of the disease.

Post Surgery

Although asymptomatic recurrence is usually incurable, a small chance does exist that a solitary metastasis could be treated definitively. Follow-up is through the urologist and/or the family doctor and it is important for the patient to be clear who is responsible.

Follow-up guidelines have been developed by consensus of the Genitourinary Cancer Site Team members, as described in Tables 6-1 to 6-7.

Table 6-1. Post Radical Nephrectomy- pT1 Tumour

Frequency	Investigations
q12 months	History & physical, LFTs, creatinine, electrolytes including Ca^{2+}, alk phos, Chest X-ray, abdominal ultrasound, test for proteinuria per 24 hr

Table 6-2. Post Radical Nephrectomy- pT2 Tumour

Year	Frequency	Investigations
1-3	q6 months	History & physical, LFTs, creatinine, electrolytes including Ca^{2+}, alk phos, Chest X-ray
1-3	q12 months	Abdominal ultrasound or CT scan of abdomen & pelvis, test for proteinuria per 24 hr
then	q12 months	History & physical, LFTs, creatinine, electrolytes including Ca^{2+}, alk phos, Chest X-ray, abdominal ultrasound or CT scan of abdomen & pelvis, test for proteinuria per 24 hr

Table 6-3. Post Radical Nephrectomy- pT3 Tumour

Year	Frequency	Investigations
1-3	q6 months	History & physical, LFTs, creatinine, electrolytes including Ca^{2+}, alk phos, Chest X-ray, abdominal ultrasound or CT scan of abdomen & pelvis
1-3	q12 months	Test for proteinuria per 24 hr
then	q12 months	History & physical, LFTs, creatinine, electrolytes including Ca^{2+}, alk phos, Chest X-ray, abdominal ultrasound or CT scan of abdomen & pelvis, test for proteinuria per 24 hr

Table 6-4. Post Partial Nephrectomy for Sporadic Renal Cell Carcinoma - pT1 Tumour

Frequency	Investigations
q12 months	History & physical, LFTs, creatinine, electrolytes including Ca^{2+}, alk phos, Chest X-ray, CT scan of abdomen & pelvis

Table 6-5. Post Partial Nephrectomy for Sporadic Renal Cell Carcinoma - pT2 Tumour

Frequency	Investigations
q12 months	History & physical, LFTs, creatinine, electrolytes including Ca^{2+}, alk phos, Chest X-ray, CT scan of abdomen & pelvis

Table 6-6. Post Partial Nephrectomy for Sporadic Renal Cell Carcinoma - pT3 Tumour

Year	Frequency	Investigations
1-2	q6 months	CT scan of abdomen & pelvis
1-2	q12 months	History & physical, LFTs, creatinine, electrolytes including Ca^{2+}, alk phos, Chest X-ray
then	q12 months	History & physical, LFTs, creatinine, electrolytes including Ca^{2+}, alk phos, Chest X-ray, CT scan of abdomen & pelvis

Table 6-7. VonHippel-Lindau Syndrome

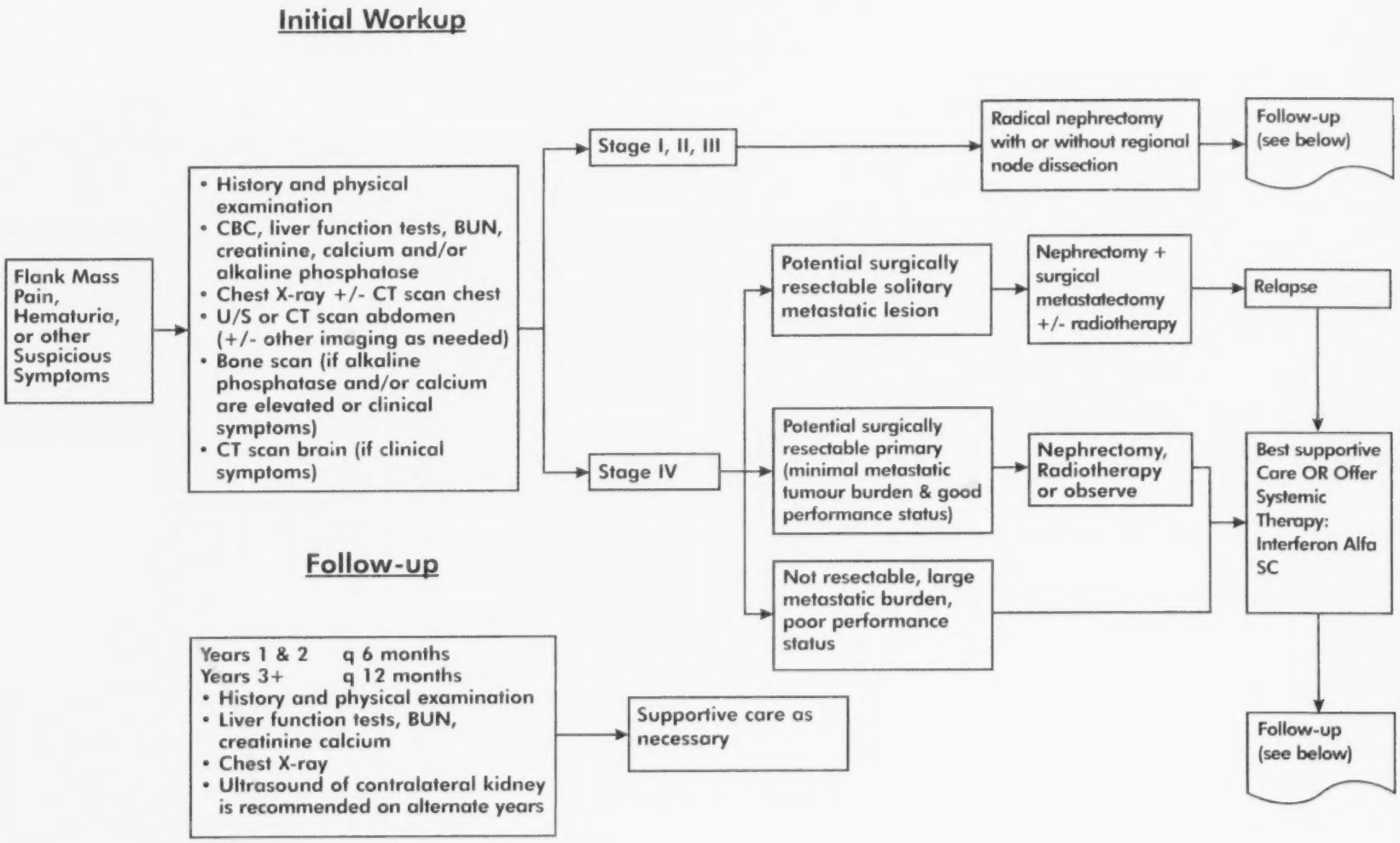
Frequency	Investigations
q6 months	CT scan of abdomen & pelvis
q12 months	History & physical, opthamological examination, urinary catecholamines
q24 months	MRI scan of central nervous system
periodic	Auditory exams

Part 7. Supportive Care Issues

Supportive Care issues are as important in the care of a cancer patient as the actual treatment. Each patient should be regularly assessed for emotional concerns and if necessary, referred to the appropriate professional. The GU Site Team will be developing supportive care guidelines specific to kidney cancers in the future.

Pain and symptom management is also important. The Supportive Care Cancer Site Team of *Cancer Care Nova Scotia* is in the process of developing guidelines for nausea and vomiting, oral care and pain control. These guidelines will be widely-circulated and available on our website when approved.

Part 8- Practice Pathway for the Management of Kidney Cancer


Initial Workup
Flank Mass Pain, Hematuria, or other Suspicious Symptoms
• History and physical examination
• CBC, liver function tests, BUN, creatinine, calcium and/or alkaline phosphatase
• Chest X-ray +/- CT scan chest
• U/S or CT scan abdomen (+/- other imaging as needed)
• Bone scan (if alkaline phosphatase and/or calcium are elevated or clinical symptoms)
• CT scan brain (if clinical symptoms)
Stage I, II, III
Radical nephrectomy with or without regional node dissection
Follow-up (see below)
Stage IV
Potential surgically resectable solitary metastatic lesion
Nephrectomy + surgical metastatectomy +/- radiotherapy
Relapse
Potential surgically resectable primary (minimal metastatic tumour burden & good performance status)
Nephrectomy, Radiotherapy or observe
Not resectable, large metastatic burden, poor performance status
Best supportive Care OR Offer Systemic Therapy: Interferon Alfa SC
Follow-up (see below)
Follow-up
Years 1 & 2 q 6 months
Years 3+ q 12 months
• History and physical examination
• Liver function tests, BUN, creatinine calcium
• Chest X-ray
• Ultrasound of contralateral kidney is recommended on alternate years
Supportive care as necessary

Part 9. Guideline Development Process

The Genitourinary (GU) Cancer Site Team of *Cancer Care Nova Scotia* developed this guideline through consensus using current literature and guidelines developed at other Canadian centres.

The final draft of the guideline was circulated to all oncologists, urologists and Chiefs of Pathology in Nova Scotia, New Brunswick and Prince Edward Island for their review and comments. GU team members and oncologists in Nova Scotia known not to treat kidney cancer were excluded from the survey. Comments were anonymously received from 18 respondents (20% response rate). Their comments were carefully considered and appropriate changes were made. The responses to key questions from the survey can be found at the end of this section. The GU team would like to thank everyone who took the time to review the draft guideline and return the survey.

The approved guideline will be circulated in hard copy to all oncologists and urologists as well as to the cancer chemotherapy clinics, regional hospital pharmacies and Chiefs of Pathology in Nova Scotia. Copies will also be made available to oncologists and urologists in Prince Edward Island and New Brunswick. Others who are interested may request hard copies by contacting *Cancer Care Nova Scotia* at 1-866-599-2267. The approved guideline will also be available on the *CCNS* website (www.cancercare.ns.ca).

The guideline will be reviewed three years after approval or revised as necessary before then as new evidence becomes available. The most recent version of this guideline will always be available on the *CCNS* website.

The development of this guideline was funded indirectly by *CCNS* via a stipend for the GU Cancer Site Team's operations. *CCNS* staff also support the guideline development process. *CCNS* directly funded the design, printing and dissemination of the guideline survey as well as the approved guideline. The views and interests of *CCNS* have not influenced the GU Cancer Site Team's recommendations in this guideline.

9.1 Key Results from Survey Review

88 questionnaires mailed to all urologists, medical and radiation oncologists and Chiefs of Pathology in Nova Scotia, New Brunswick, and Prince Edward Island.

8 returned "Not delivered"

18 surveys completed and returned

18/80 (22% response rate)

Respondents by Specialty and Province

	New Brunswick	Nova Scotia	Prince Edward Island	Total and Percent
Urology	2	4		6 (33%)
Medical Oncology	2		1	3 (17%)
Pathology	1	4	1	6 (33%)
Radiation Oncology	3			3 (17%)
Total and Percent	8 (44%)	8 (44%)	2 (11%)	18 (100%)

Q1 Is the Guideline relevant to your practice?

Total Responses 18 - Yes 15 No 3

Q2 A guideline on this topic will be useful to clinicians.

Total Responses 16 - Strongly Agree 8 Agree 8

Q3 I agree with the guideline.

Total Responses 16 - Strongly Agree 5 Agree 10
Disagree 1

Q6 Would you use this guideline in your own practice?

Total Responses 17 - Yes 17

Q7 In your opinion, this guideline should be disseminated to all appropriate practitioners in Nova Scotia.

	Yes	No	Unsure
Total Responses 16 -	12	3	1

9.2 Genitourinary Cancer Site Team Members

David Bell	Urologic Oncology Capital Health (Surgical Oncology Lead)
Lori Wood	Medical Oncology Lead Capital Health (Co-Chair)
Derek Wilke	Radiation Oncology Lead Capital Health (Co-Chair)
Tetteh Ago	Radiation Oncology Cape Breton District Health Authority
Lorrie Bambury	Oncology Nurse Capital Health
Larry Broadfield	Manager, Systemic Therapy Program *CCNS*
Angela Dalrymple	Nurse Educator Capital Health
Heather Dixon	Oncology Nurse Capital Health
Mark Dorreen	Medical Oncology Capital Health
Donna Grant	Nurse Educator Capital Health
Rekha Gupta	Pathology Capital Health
Paul Joseph	Radiation Oncology Capital Health
Cheryl Lamkey	Oncology Nurse Capital Health
Heather MacKenzie	Cancer Site Team Secretary *CCNS*
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Ricardo Rendon	Urologic Oncology Capital Health
Leonard Reyno	Medical Oncology Capital Health
Dorianne Rheaume	Radiation Oncology Capital Health
Robert Rutledge	Radiation Oncology Capital Health
Brenda Sabo	Surgical Oncology Coordinator *CCNS*
Marlene Sellon	Oncology Pharmacy *CCNS*

Appendix I

Guidelines for the Role of Interferon-Alfa (IFN-a) in Metastatic Renal Cell Carcinoma (RCC)
Evaluation Summary Report

Drug Name:	Interferon-alpha (IFN-a)
Indication:	Metastatic Renal Cell Carcinoma (RCC)
Interpretive Summary:	The 5-year survival rate for patients with metastatic RCC is poor, ranging from 0%-20%. While nephrectomy (or radiotherapy for inoperable patients) may be offered to patients with localized RCC, these interventions are of little or no value when the RCC has advanced to metastatic disease. Systemic therapy with chemotherapy or hormonal agents has not been effective, and is not offered to patients. Immunotherapy, with IFN-a has demonstrated a modest but proven survival benefit in patients with metastatic RCC. IFN-a represents a reasonable option to offer patients with this disease.
Clinical Information: Clinical Efficacy Summary:	The Cochrane Review 2001 reported the interferon arm of trials compared to control arms was consistently better. A pooled response rate (RR) of 13.9% for IFN-a versus 2.2% for a variety of controls. Average median survival was 2.6 months longer for IFN-a than the controls. A reduction of 1 year mortality by 27%, and a 22% risk reduction for death during the first 2 years compared to non-immunotherapy controls was reported. Medical Research Council (MRC) trial (Ritchie et al 1999) reported an absolute improvement in 1 year survival of 12% with the use of IFN-a. The median survival time was 2.5 months longer for IFN-a than the control group. Meta-analysis (n=525 patients) by Heinberg et al 1999 concluded that IFN-a improved the RR and overall survival (OS) compared with regimens without IFN.
Quality of Evidence:	The bulk of material presented - Level I and Level II evidence (Published in peer reviewed journals or in abstract form). Quality of Life (QOL) data reported in the MRC trial. Selection criteria for the Cochrane Review included randomized controlled trials that selected patients with RCC which utilized an immunotherapeutic agent in at least one study arm and reported response or survival. The meta-analysis (Hernberg et al 1999) compared all available randomized trials which compared regimens with or without IFN-a.
Glossary:	Clinical Response is measured by the Response Rate Response Rate (RR): • May include: - Complete response (CR) - disappearance of all clinical and radiological evidence of tumour; - Partial response (PR) - at least a percentage decrease in the amount of disease; - Stable disease (SD) - steady appearance of disease; - Progressive disease (PD) - a percentage increase in the amount of disease. Overall Responses (OR): • Overall "Best Response" would take into account changes in appearance of specific disease being followed. Overall Survival (OS): • The period of time from start of therapy to death.

	Time to Progression (TTP): • The time interval between initiating therapy and first documented sign of progression. **Performance Status** (Eastern Cooperative Oncology Group [ECOG]): 0 = Normal activity 1 = Symptoms but ambulatory 2 = In bed <50% of the time 3 = In bed >50% of the time 4 = 100% bedridden
Technical Information: Classification:	Biological Response Modifier AHFS 10:00 (Immunotherapy)
Manufacturer:	Schering (Interferon-alfa-2a-IntronA®); Roche (Interferon-alfa-2b-Roferon-A®)
Pharmacology	Exhibits antiproliferative effects, immunodulatory activity and inhibits viral replication.
Pharmacokinetics:	Absorption: Well absorbed SC or IM Bioavailability: SC-90% IM-83% Distribution: Vd - 31L; does not penetrate the CNS Metabolism: Hepatic and Renal Elimination: Renal, some hepatic and biliary Time to peak serum concentration: IM/SC - approximately 6-8 hours Dose Selected: The optimal dose schedule of recombinant IFN-a has yet to be determined but should be used within the range used in the larger trials showing efficacy.
Dosage and Administration:	5 million units/m^2 per day subcutaneous (SC) injections administered by patient at home.
Side Effects:	Toxicity profile of IFN-a includes fever, myalgias and asthenia (flu-like symptoms) particularly at onset of treatment. Other toxicities include nausea, diarrhea, anorexia, liver dysfunction, thrombocytopenia, leukopenia and mental confusion.
Expected Place in Therapy:	As a single agent in patients who have documented evidence of metastatic RCC, with an ECOG performance status of 0-2, who choose to receive immunotherapy as an alternative to best supportive care outside the auspices of an existing clinical trial.
Consensus of Experts:	Parameters such as performance status (PS), patient choice, other palliative options and toxicity should be considered on an individual basis.
Approvals:	GU Cancer Site Team - September 2001. QEII Health Sciences Centre - Oncology Therapy Subcommittee - September 26, 2001. QEII Health Sciences Centre - Drugs and Therapeutics Committee - November 20, 2001.
Cost Analysis:	Standard of care options would include immunotherapeutic intervention with IFN-a or supportive care. No direct cost comparison of these interventions has been performed. The cost utility of the survival benefit with a therapeutic intervention of IFN-a has not been reported.
Advantages:	Reasonable treatment option for selected patients with metastatic disease and good performance status (PS) (0-2) in a disease which offers no other treatment options other than supportive care. Overall response is the best response obtained over time. The RR is assessed after 2-3 months of therapy. Depending on the response, therapy will continue or stop.

Disadvantages:	The toxicity profile and continuous use of SC injections may deter patients from choosing such a treatment option.

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